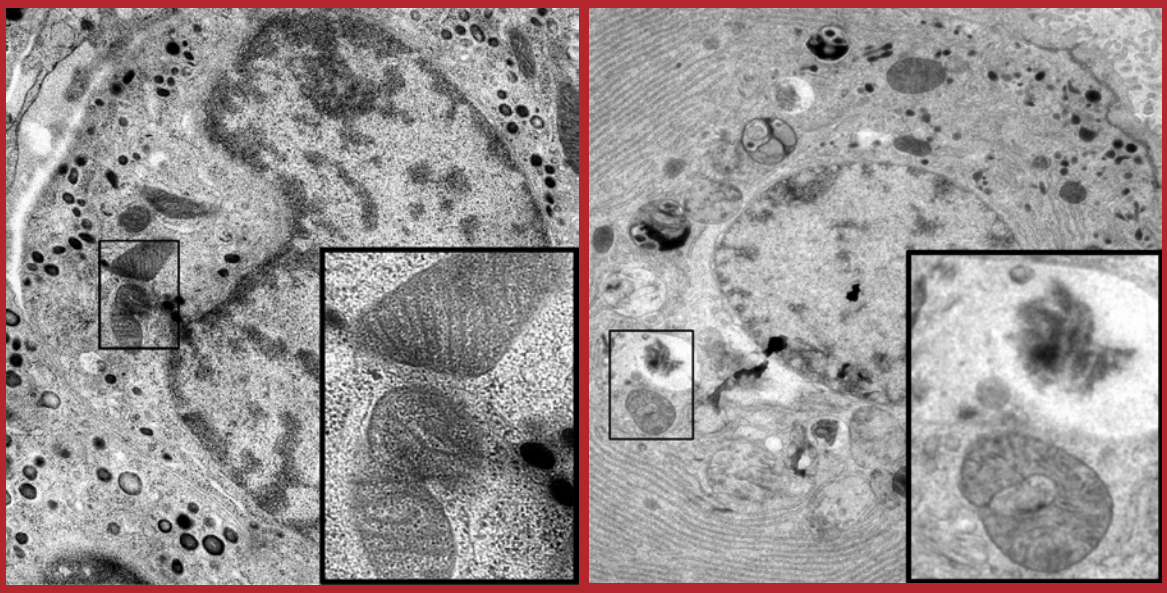


Healthy mitochondria, the “powerhouses” of the cell, are necessary for insulin-producing β (beta) cells of the pancreas to function normally. This set of high magnification transmission electron micrograph images shows how loss of the protein Clec16a in mouse β cells affects mitochondria. As shown in detail in the insets, normal, healthy mouse β cell mitochondria (left) exhibit highly ordered structural patterns, while mitochondria in β cells lacking Clec16a protein (right) appear amorphous and unhealthy. As described in this chapter, Clec16a appears to play an important role in cellular mechanisms exerting “quality control” on mitochondria. The gene encoding the human version of Clec16a is known to affect risk for type 1 diabetes, so findings from this study may help further understanding of the protein’s role in human disease.

Image courtesy of Dr. Scott A. Soleimanpour, University of Michigan, and Dr. Doris A. Stoffers, University of Pennsylvania School of Medicine. Reprinted from Cell, Vol 157, Soleimanpour SA, Gupta A, Bakay M, Ferrari AM, Groff DN, Fadista J, Spruce LA, Kushner JA, Groop L, Seeholzer SH, Kaufman BA, Hakonarson H, Stoffers DA, The diabetes susceptibility gene Clec16a *regulates mitophagy, Pages 1577-1590, Copyright 2014, with permission from Elsevier.*

Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, these diseases and conditions affect many millions of Americans and can profoundly decrease quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 29.1 million people in the United States—or 9.3 percent of the total population—and is the seventh leading cause of death.[1] Compared with people of similar age without the disease, overall rates of death are about 1.5 times higher in people with diabetes, and rates of death from cardiovascular disease are 1.7 times higher.[1] Although rates of diabetes-related complications have declined substantially in the past 2 decades, disease burden remains significant as the number of people with diabetes continues to increase.[2] Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diabetes in the United States in 2012—including costs of medical care, disability, and premature death—was $245 billion.[3] Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that is similar to type 2 diabetes but unique to pregnancy. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery.

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of diagnosed diabetes cases in adults, and the majority of diagnosed cases in children and youth.[1] It most often develops during childhood but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing β (beta) cells of the pancreas. If left untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. Thus, people with type 1 diabetes require

[1] *Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services, 2014.*

[2] *Gregg EW, et al. N Engl J Med 370: 1514-1523, 2014.*

[3] *American Diabetes Association. Diabetes Care 36: 1033-1046, 2013.*

lifelong insulin administration—in the form of multiple daily injections or *via* an insulin pump—to regulate their blood glucose levels. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. However, despite vigilance in disease management, with current technologies to test blood glucose levels and administer insulin, it is still not possible for patients to control blood glucose levels to levels achieved by functional β cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery. This includes continued development and testing of "artificial pancreas" technologies in real-world settings, as well as working to develop β cell replacement therapies, such as islet transplantation, to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.[1] The risk for developing type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Type 2 diabetes occurs at higher rates among racial and ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, and Native Hawaiians and Pacific Islanders.[1] Gestational diabetes is also a risk factor: shortly after pregnancy, 5 to 10 percent of women with gestational diabetes continue to have high blood glucose levels and are diagnosed with diabetes, usually type 2.[1]

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic β cells lose their ability to secrete enough insulin to restore balance, and the timing of insulin secretion becomes abnormal, causing blood glucose levels to rise. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 86 million U.S. adults who have a condition called "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.[1] This population is at high risk of developing diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight. Moreover, follow-up research has shown that this benefit of reduced diabetes risk can persist for at least 10 years.

Type 2 diabetes was previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects youth from racial and ethnic minority populations in the United States. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. For example, the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial showed that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with both the duration of diabetes and control of blood glucose levels; thus, those with early disease onset are at greater risk with respect to complications than those who develop the disease later in life. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could lead to a cycle of ever-growing rates of diabetes. Therefore, the advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

The NIDDK is supporting research to better understand metabolism and the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the

NIDDK's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

UNDERSTANDING RISING DIABETES RATES IN AMERICAN YOUTH

Rates of Diabetes Increasing in U.S. Youth: The SEARCH for Diabetes in Youth study has provided new data on the prevalence (proportion of the population with the disease) and incidence (proportion of the population who develop the disease each year) of both type 1 and type 2 diabetes in a geographically and racially/ethnically diverse group of children and teens. This information will help researchers identify trends and potential causes of the disease, which is a significant health problem in the United States.

SEARCH researchers found that between 2001 and 2009, both types of diabetes became increasingly prevalent in youth under 20 years of age. Type 1 diabetes remains the predominant form in youth, with about four times as many youth affected with type 1 diabetes than with type 2 diabetes. Except in American Indians, type 1 diabetes accounts for nearly all diabetes in children under the age of 10. However, prevalence of type 2 diabetes is increasing more rapidly. Overall, the proportion of youth with type 2 diabetes rose by 30.5 percent while the proportion with type 1 diabetes rose by about 21 percent.

The increase in type 1 diabetes prevalence was seen in both sexes and in White, Black, Hispanic, and Asian Pacific Islander youth. Historically, type 1 diabetes has been considered to affect primarily non-Hispanic White youth; the new data demonstrate that it is also an increasing burden for minority youth. Additionally, SEARCH found that rates of new cases of type 1 diabetes increased by about 2.7 percent per year in non-Hispanic White youth, with the increase seen in both males and females and in all age groups except the youngest (0- to 4-year-olds).

Once considered a disease of adults, type 2 diabetes has emerged as a significant health issue among U.S. youth, spurred by the prevalence of obesity, a strong risk factor for this form of diabetes. SEARCH found significant increases in type 2 diabetes prevalence between 2001 and 2009 in both sexes, all age groups, and in White, Hispanic, and Black youth. While there were no significant changes for Asian Pacific Islanders and American Indians, American Indians had rates 10-fold greater than in White youth. Overall, the highest prevalence was found in American Indians, followed by Black, Hispanic, and Asian Pacific Islander youth, with lowest prevalence in White youth. These results demonstrate the increasing burden of type 2 diabetes on youth of minority racial/ethnic groups in the United States.

Increases in both type 1 and type 2 diabetes prevalence and incidence in youth are worrying because these populations face unique challenges in managing their diabetes and may be at greater risk of diabetic complications later in life due to their long disease duration. Collectively, the SEARCH findings provide critical information on recent trends in diabetes in U.S. youth and will help inform future planning, research, and policies aimed at relieving the burden of diabetes.

Dabelea D, Mayer-Davis EJ, Saydah S,…Hamman RF; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 311: 1778-1786, 2014.

Lawrence JM, Imperatore G, Dabelea D,…D'Agostino RB Jr.; for the SEARCH For Diabetes In Youth Study Group. Trends in incidence of type 1 diabetes among non-Hispanic white youth in the United States, 2002-2009. Diabetes 63: 3938-3945, 2014.

GENETICS AND GENETIC REGULATION OF TYPE 2 DIABETES

Rare Genetic Mutations That Protect Against Type 2 Diabetes Suggest Possible Approach for Treating the Disease: Researchers examining multiple different ethnic populations have identified

rare mutations in the gene *SLC30A8* that appear to significantly reduce risk for type 2 diabetes. Most mutations have little or no impact on health, and some have detrimental health effects, particularly if they interfere with the proper function of an important gene; but occasionally mutations may be found that reduce the function of a gene (referred to as loss-of-function mutations), yet provide a detectable health benefit. Such mutations offer a particularly alluring possibility: the potential to design medicines that specifically reduce the activity of the gene, or of the protein it encodes, in a way that may be similarly beneficial for people who do not have the protective mutation. To identify possible loss-of-function mutations that might protect against type 2 diabetes, the research team focused on genes already thought to be involved in diabetes because common variations in or near the genes are known to be associated with modest differences in risk for the disease. Among nearly 14,000 people, almost half of whom had type 2 diabetes, they found a mutation that truncates the protein encoded by the *SLC30A8* gene in 21 people without diabetes, but in only 7 people who had the disease. Expanding their analysis to include about 150,000 people of multiple racial/ethnic backgrounds (African American, European, South Asian, and East Asian), the researchers found more protein-truncating mutations in *SLC30A8*. Overall, they found that these rare mutations were about three times as likely to occur in people who did not have type 2 diabetes as in those who did, strongly suggesting that *SLC30A8* loss-of-function mutations protect against type 2 diabetes.

Surprisingly, this was just the opposite of the previous scientific consensus about the gene and its function. *SLC30A8* encodes a protein called ZnT8 that helps bring zinc into cells. ZnT8 is produced at high levels in the insulin-producing β (beta) cells of the pancreas, where zinc is known to play an important role: it stabilizes insulin stored within the cells prior to secretion. In humans, there are two common *SLC30A8* variants that both encode full-length ZnT8 proteins, although the ZnT8 proteins produced by the two variants are slightly different from one another. One of these two common variants was previously associated with a modest increase in risk for type 2 diabetes, and was also thought to reduce zinc transport. Taken together, the results of the newer and older studies represent something of a puzzle: rare mutations that completely inactivate one of a person's two copies of *SLC30A8* lower risk of type 2 diabetes, while a much more common version of *SLC30A8* that encodes a lower-activity form of ZnT8 raises disease risk. Further research is needed to explain this paradox and to determine whether type 2 diabetes can be better treated or prevented through therapeutic modulation of ZnT8 function.

Flannick J, Thorleifsson G, Beer NL,...Altshuler D. Loss-of-function mutations in SLC30A8 *protect against type 2 diabetes. Nat Genet 46: 357-363, 2014.*

Micro Molecules May Have Big Role in Type 2 Diabetes: Researchers identified microRNAs that may be factors in type 2 diabetes. MicroRNAs (miRNAs) are molecules that specifically regulate gene expression—whether a gene is "turned on"—and, in many cases, leads to the production of a protein. Specifically, miRNAs block the production of proteins by interfering after the gene is turned on. Not all genes, however, encode proteins. For example, some genes encode miRNAs. Because each type of miRNA is present in numerous copies in a cell and can specifically regulate expression of multiple different protein-encoding genes, cells can use miRNAs to downregulate several "targets" simultaneously. miRNAs have been shown to affect the development and progression of several diseases and, therefore, are speculated to have a role in type 2 diabetes. In this study, scientists aimed to identify miRNAs that are involved in type 2 diabetes. They catalogued all the miRNAs found in pancreatic islet cells from people with type 2 diabetes and from people without the disease, and found that some miRNAs are produced in greater abundance in the islets of people with type 2 diabetes, and some are produced at lower levels. Interestingly, several of the miRNAs produced at lower levels are encoded by genes in the same region of the genome.

By studying this cluster of genes that encode the miRNAs, the scientists gathered information about how these miRNAs might influence development of type 2 diabetes. Looking at different types of

islet cells, they discovered that the miRNAs in this cluster are highly and specifically produced in normal β (beta) cells and repressed in β cells from people with type 2 diabetes. The repression, the researchers discovered, correlated with the increased presence of an "epigenetic" mark near the cluster. Epigenetics refers to a phenomenon in which there are changes in gene activity without alteration of the genome sequence. This phenomenon can be temporary or fixed, and can even be passed from generation to generation in families. Thus, along with genetic factors that increase type 2 diabetes risk due to genome sequence variants, epigenetic marks may also increase risk for developing this disease and may explain, in part, why type 2 diabetes runs in families. Therefore, the increased presence of the epigenetic mark near this cluster of miRNA genes could be a heritable risk factor for type 2 diabetes.

Additional experiments showed that the miRNAs in this cluster regulate gene expression and, consequently, the production of proteins involved in many key biological processes, including cell death, a process that can contribute to the development of type 2 diabetes. These results suggest that, in people with type 2 diabetes, the miRNA cluster is "turned off," leading to decreased production of the miRNAs and, as a consequence, increased production of proteins that cause β cell dysfunction and cell death. This early study indicates that miRNAs may play a role in type 2 diabetes development, progression, or both. Further research is needed to elucidate the detailed role of miRNAs in type 2 diabetes and to determine whether increasing activity of specific miRNAs could be a therapeutic strategy to protect against the disease and its progression.

Kameswaran V, Bramswig NC, McKenna LB,...Kaestner KH. Epigenetic regulation of the DLK1-MEG3 *microRNA cluster in human type 2 diabetic islets. Cell Metab 19: 135-145, 2014.*

A Genetic Mutation That Affects Fat Metabolism Can Bring on Type 2 Diabetes: Recent research suggests that a protein involved in the metabolism of fat may play a critical role in helping prevent type 2 diabetes. Although overweight and obesity are clearly associated with an elevation in risk for type 2 diabetes, the precise way or ways in which excess body fat contributes to development of the disease remain a subject of considerable scientific debate and investigation. According to one major hypothesis, defects in fat metabolism and increased levels of metabolic intermediates in the fat utilization process may adversely affect insulin sensitivity and/or production. To explore this possibility, researchers examined genes encoding many of the proteins involved in fat metabolism in Amish families in which some family members had type 2 diabetes. An advantage of conducting this kind of study among the Amish is that they have a relatively homogenous, non-mechanized lifestyle. As a result, differences in metabolic health between Amish individuals are more likely to be due to genetic factors than to diet or exercise. Working with this unique group of people, researchers identified a mutation present in about 5.2 percent of Amish people tested that was strongly associated with type 2 diabetes risk. This mutation affects a gene that encodes a protein called hormone-sensitive lipase (HSL). The mutation is also found in about 0.2 percent of non-Amish people of European descent.

HSL plays a vital role in liberating triglycerides—the primary type of fat stored by the body in adipose (fat) tissue—when they are needed for energy. Thus, one might expect that having insufficient HSL would lead to an accumulation of excess fat throughout the body, promoting obesity. Surprisingly, however, the researchers found that having one mutated copy of the HSL gene and one normal copy of the gene (effectively cutting levels of the HSL protein in half) was associated specifically with an increase of fat stored in the liver, though not elsewhere, and with unhealthy levels of triglycerides and other fats in the blood. Importantly, the mutation promoted significant insulin resistance, and almost doubled the risk for type 2 diabetes. In addition, the researchers identified four individuals who lacked any normal copy of the gene, making it possible to examine health effects of not being able to make any HSL protein at all. All four developed type 2 diabetes before the age of 50, and had sharply elevated fasting triglyceride levels and slow triglyceride clearance after a high-fat meal, compared to people with functional

HSL protein. These findings mark HSL as an important metabolic regulator. Further research will be needed to determine how the protein helps prevent type 2 diabetes, and whether its activity can be safely modulated to help treat or prevent the disease.

Albert JS, Yerges-Armstrong LM, Horenstein RB,...Damcott CM. Null mutation in hormone-sensitive lipase gene and risk of type 2 diabetes. N Engl J Med 370: 2307-2315, 2014.

INSIGHTS INTO TYPE 2 DIABETES TREATMENTS

Comparing Surgical and Non-surgical Treatments for Type 2 Diabetes in Adults Who Have Mild or Moderate Levels of Obesity: Two small clinical trials found that after 1 year of treatment, bariatric surgery may be more effective than non-surgical approaches for treating type 2 diabetes in adults who have mild or moderate levels of obesity. They also identified factors to be considered in planning further research. Previous studies demonstrated the benefits of bariatric surgical procedures for weight loss and for ameliorating type 2 diabetes, at least in the short-term, in individuals with either extreme obesity (defined as a "body mass index," or BMI, of 40 or more) or somewhat lower levels of obesity (BMI 35 to 40). However, there has been only limited research on this surgery in people with milder levels of obesity (BMI 30 to 35). Thus, investigators recently conducted small clinical trials to gain preliminary insights into the risks and benefits of bariatric surgery, compared to non-surgical interventions, for type 2 diabetes in people with various levels of obesity. The trials also aimed to elucidate the challenges to be addressed in designing a more extensive study with larger numbers of participants.

In one of the clinical trials, investigators randomly assigned 69 volunteers to receive either bariatric surgery or an intensive lifestyle intervention for weight loss, and then compared health outcomes after a year. All of the participants had type 2 diabetes and mild to moderate levels of obesity (BMI 30 to 40); most were women. Those assigned to surgery received either a Roux-en-Y gastric bypass (RYGB) procedure or laparoscopic adjustable gastric banding (LAGB). The intensive lifestyle intervention involved both diet and exercise and was delivered in an individualized format. After 1 year, about 50 percent of the individuals in the RYGB group and 27 percent of those in the LAGB group had partial diabetes remission. Their blood glucose (sugar) levels, although not quite normal, were no longer in the range of diabetes; and they were able to discontinue their diabetes medications. Several individuals in each surgical group achieved complete remission of their diabetes—normal blood glucose levels without need for diabetes medications. None of the people in the lifestyle intervention group had partial or complete diabetes remission. Participants in all of the groups lost weight; those in the RYGB group had the greatest weight loss. However, several individuals in the RYGB and LAGB groups experienced complications, including a surgery-related ulcer and dehydration.

In the other clinical trial, investigators randomly assigned volunteers with type 2 diabetes and obesity (BMI 30 to 42) to receive either RYGB surgery or a lifestyle and medical intervention of diet and exercise, delivered in group sessions, with a weekly medication adjustment plan. Of the 38 participants analyzed in the study, a majority were women. After 1 year, 58 percent of the individuals in the RYGB group, but only 16 percent of those in the lifestyle and medical therapy group, saw their blood glucose levels improve to the target for glucose control chosen as the study outcome. Weight loss was greater in the RYGB group as well. Assessing the safety of the interventions, the researchers noted several serious adverse events among participants in the RYGB surgery group, including ischemic heart disease requiring coronary artery bypass surgery and depression with attempted suicide. In the non-surgical group, a few individuals experienced near-fainting.

The researchers also described important "lessons learned" from these clinical trials. A major challenge was recruitment. Each research team screened hundreds of potential volunteers, but only about 1 of every 10 individuals screened for one study and 1 of 20 screened for the other study were both eligible and interested in participating. In each study, several individuals stopped

participating after being assigned to a group, but before receiving the intervention. Costs also posed a challenge because insurers do not currently cover bariatric surgery for people with lower levels of obesity. For these trials, the investigators obtained some funding for the surgical procedures either from their academic medical center or industry. The research aspects were supported by the NIH. Finally, the types of bariatric surgery used in clinical practice continue to change over time; it may thus be valuable to study different surgical procedures in the future.

In summary, these small clinical trials add to preliminary evidence that bariatric surgery may be more effective than current non-surgical treatments for type 2 diabetes in individuals with mild to moderate levels of obesity. This research also highlights challenges to be met in designing larger and longer-term studies in the future, to gain more definitive data on risks and benefits.

Courcoulas AP, Goodpaster BH, Eagleton JK,...Jakicic JM. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg 149: 707-715, 2014.

Halperin F, Ding SA, Simonson DC,...Goldfine AB. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 149: 716-726, 2014.

For more information on bariatric surgery, please see the Obesity chapter.

New Explanation for the Glucose-lowering Effect of the Diabetes Medication Metformin: New research suggests that metformin, the first-line therapy for type 2 diabetes, works by directly inhibiting the activity of a key metabolic enzyme. In addition to its role as a diabetes medication, metformin is a safe and effective treatment for prediabetes and polycystic ovarian disease, and is being studied as a potential therapy for cardiovascular disease and some cancers. While safe, inexpensive, and highly effective for type 2 diabetes, its use is limited due to gastrointestinal side effects in some people, genetic variation causing inter-individual differences in response, and safety concerns in people with chronic kidney disease. For these reasons, there is considerable interest in finding alternative treatments that act in the same way as metformin. However, although metformin has been widely used for decades, its molecular mechanism has remained elusive and is a subject of considerable scientific debate.

Metformin is known to lower blood glucose (sugar) by reducing the amount of glucose produced by the liver and released into the blood. While it is agreed upon that energy metabolism is at the center of metformin's mechanism of action, the precise target of metformin within the complex processes that take place in cells to convert energy from nutrients into forms needed to fuel cellular activity has not been established. Now, a new mode of action has been suggested by the finding that metformin directly inhibits the action of mitochondrial glycerophosphate dehydrogenase (mGPD), an enzyme that helps make it possible to move molecules derived from stored fat into the mitochondria for conversion into glucose. This enzyme is not among those previously studied in connection with metformin action, although mice deficient in this enzyme do not develop elevated glucose levels on a high-carbohydrate diet. Importantly, researchers found that experimentally reducing the amount of mGPD in cells lowered blood glucose levels at a speed and to an extent similar to what is observed with metformin treatment. Further, they found that in male rats lacking mGPD, metformin did not result in any further lowering of blood glucose, suggesting that metformin's effect on this enzyme may account for much of the medicine's glucose-lowering properties. Because these experiments were performed in rodents, the researchers tested the effect of metformin on a purified human form of the enzyme and found similar inhibition.

These findings identify mGPD as a key facilitator of liver glucose production and suggest that if safe new medicines that target the same enzyme in people can be identified, they might represent effective

glucose-lowering treatments for individuals who cannot tolerate metformin, or in whom the drug is not effective.

Madiraju AK, Erion DM, Rahimi Y,...Shulman GI. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 510: 542-546, 2014.

ADVANCING TECHNOLOGY IN DIABETES MANAGEMENT

Artificial Pancreas Technologies Excel in Real-world Tests: Two studies propelled progress toward development of artificial pancreas technologies, a promising treatment for people with type 1 diabetes. People with this disease do not produce insulin, a hormone made by the pancreas that regulates the level of glucose (sugar) in the blood and delivers glucose to the cells of the body. Therefore, they have to receive injections of insulin on a daily basis or wear an insulin pump. Too little insulin can lead to high blood glucose, which increases the risk of diabetic complications. Too much insulin, however, is dangerous as well, resulting in low blood glucose (hypoglycemia) which can lead to coma or death, a particular concern during sleep. People with type 1 diabetes walk a tightrope to keep their blood glucose levels within a healthy range and continually must check their levels with fingerstick tests or a continuous glucose monitor. With these burdensome methods it is difficult to achieve recommended levels of blood glucose control. An artificial pancreas, or a closed-loop system, could help people achieve these recommended levels, as well as alleviate patient burden, by linking three technologies: a glucose-sensing component, an insulin delivery device, and a computer that calculates the amount of insulin needed in response to the blood glucose level.

Early artificial pancreas clinical trials took place in hospital settings and used laptop computers to run the technology, restricting the activities of participants. Recent trials have built on the success of the inpatient trials, testing ambulatory devices in real-world settings, with some of the challenges of everyday life—such as eating a variety of foods, which raise blood glucose to different levels, and participating in various forms of physical activity, which lower blood glucose. In one study, scientists achieved exciting results testing unsupervised overnight home use of a closed-loop system in 16 adolescents with type 1 diabetes for 21 nights. During the day, the participants used standard glucose sensor and pump therapy and there were no restrictions placed on their daytime activities—they participated in school and other activities, including sports, and ate a regular diet. At night, they used the closed-loop system, controlling it on their own, with minimal supervision on only the first night. Compared to a control period during which the standard glucose sensor and pump therapy were used both day and night, unsupervised closed-loop control at night improved participants' glucose control during the day and night, and also reduced the number of episodes of nighttime hypoglycemia. The success of this study illustrates the high potential for closed-loop technology to be translated into clinical care.

In another study, researchers tested a wearable, automated, bihormonal "bionic" pancreas—one that releases both insulin and its counteracting hormone, glucagon. By including both of these hormones, the scientists hope to replicate more closely the sophisticated glucose control of the biological pancreas. They tested the bionic pancreas in two scenarios, one with adults with type 1 diabetes in Boston and one with adolescents with type 1 diabetes at diabetes summer camp. Twenty adults wore this device, which was controlled by a cell phone, around Boston for 5 days and nights, unrestricted in their activities. They ate in restaurants, exercised at gyms, and stayed in a hotel and were accompanied by study staff. Thirty-two adolescents at diabetes summer camp wore the same device for 5 days. In both scenarios, compared to usual care (insulin pump), participants had lower mean glucose levels and reduced episodes of hypoglycemia. In fact, the bionic pancreas allowed nearly all participants to achieve recommended levels of blood glucose control.

With the encouraging results of these two studies, additional, larger trials of artificial pancreas technologies could pave the way toward conducting pivotal trials needed for U.S. Food and Drug

Administration approval of these technologies. Further development of this technology will also improve efficacy and usability, but this research highlights the ability of artificial pancreas technologies to help people with type 1 diabetes achieve good blood glucose control and lead freer, healthier lives.

Hovorka R, Elleri D, Thabit H,…Dunger DB. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care 37: 1204-1211, 2014.

Russell SJ, El-Khatib FH, Sinha M,…Damiano ER. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 371: 313-325, 2014.

BETA CELLS AND DIABETES

Discovery of New Ways To Produce Beta Cells: Two different research groups in the NIDDK's Beta Cell Biology Consortium have made important steps forward with research on generating insulin-producing β (beta) cells from other types of cells, accelerating progress toward potential new therapies for type 1 diabetes. In people with type 1 diabetes, the β cells are destroyed erroneously by the immune system, resulting in people with the disease having to rely on administration of insulin. Although administration of insulin is a life-saving therapy, it does not replicate the biology of the β cells. Therefore, a goal of type 1 diabetes research is to generate ways to replace the lost β cells. Years of research into β cell biology has focused on ways of producing β cells in the laboratory or of regenerating β cells within a person's pancreas.

One research group determined a method to produce β cells from human stem cells in the laboratory, an advance that could bolster islet transplantation as a therapy for type 1 diabetes. Islet transplantation—during which pancreatic islets, including β cells, are transplanted into people whose own β cells are destroyed—is a promising experimental treatment for type 1 diabetes. However, islet transplantation has been hindered, in part, by the limited quantities of donor islets and the side effects of immunosuppression. The field of stem cell biology has offered hope that islets could be produced in the laboratory. Stem cells are pluripotent, meaning they are able to produce any type of cell in the body, and induced pluripotent stem cells can be made by "reprogramming" adult cells. Previous attempts to produce islets in the lab by differentiating, or maturing, human stem cells into β cells have generated cells that produce insulin, but which lack several important β cell-like qualities, such as a finely tuned response to changing glucose (sugar) levels.

Drawing on this previous research, scientists sought to improve on these results by testing over 70 chemical compounds in over 150 combinations. They developed an optimized, multistep process utilizing 11 of these compounds in a precise sequence over the course of 4 to 5 weeks. By the end of this process, the researchers had coaxed large numbers of both human embryonic stem cells[1] and induced pluripotent stem cells (which can be made from adult cells, including cells from those with type 1 diabetes) into a state that closely resembles naturally occurring β cells. Importantly, these "stem-cell-derived β (SC-β) cells" are similar to pancreatic β cells and respond to fluctuating glucose levels by increasing or decreasing secretion of insulin, as appropriate. To test whether they might be therapeutically useful, the researchers transplanted human embryonic SC-β cells into mice genetically engineered to display type 1 diabetes-like symptoms. After 2 weeks, the SC-β cells were producing significant amounts of insulin in response to glucose and prevented the mice from developing dangerously high blood glucose levels.

Although the process will need to be adapted for large-scale manufacturing, and further tests must be conducted to determine if SC-β cells can be a long-term replacement for β cells in people, this dramatically improved process for making large amounts of β cells is a promising step toward developing therapeutic stem cell therapies. SC-β cell technology may lead to advances in treating diabetes and in artificial organ

[1] *The NIH supports research using human embryonic stem cells within the* NIH Guidelines for Human Stem Cell Research.

development, especially if ways to protect newly transplanted β cells from the autoimmune attack are developed. Additionally, SC-β cells offer a valuable new resource for investigating β cell biology and disease modeling, as well as opportunities for drug screening and testing novel potential therapies.

The second research team discovered that δ (delta) cells within the pancreas are capable of being reprogrammed into β cells, another potential way to restore the β cells lost in people with type 1 diabetes. Pancreatic islets are composed of several types of hormone-producing cells: insulin-producing β cells, glucagon-producing α (alpha) cells, and somatostatin-producing δ cells. Previous research in mice demonstrated that, following targeted destruction of the β cells, the pancreas can recover the ability to produce insulin. How this recovery occurs has not been well-understood, but the biological processes potentially could be adapted to restore insulin production in people with type 1 diabetes.

The researchers had previously demonstrated that, following β cell injury, α cells were able to convert directly to "β-like" cells and produce insulin in adult male mice. In this new advance, scientists discovered a novel pathway for the generation of "β-like" cells following a β cell injury in juvenile male mice, which differs from the α cell-dependent pathway in adult male mice. They found that a different pathway occurs in juvenile mice than in adults: δ cells revert to an uncommitted precursor-like state, replicate, and then some convert to β-like cells and acquire the ability to produce insulin. Further research will determine whether either or both the adult and juvenile β cell regeneration processes are active in humans and whether these processes can be adapted to regenerate lost β cells in people with type 1 diabetes. As these experiments showing δ cell conversion to β cells were performed in male mice, future studies may show if this process also occurs in females, and new ways to protect regenerated β cells from immune attack will need to be developed, as well.

These two studies are important steps forward in β cell biology, biotechnology, and the treatment of type 1 diabetes. Future studies will be necessary to determine whether these new ways of producing β cells will be useful in developing human therapies. Together, these findings offer hope that new β cells can be generated to replace those lost in type 1 diabetes and suggest exciting opportunities to improve the lives of people with this disease.

Pagliuca FW, Millman JR, Gürtler M,...Melton DA. Generation of functional human pancreatic β cells in vitro. *Cell 159: 428-439, 2014.*

Chera S, Baronnier D, Ghila L,...Herrera PL. Diabetes recovery by age-dependent conversion of pancreatic δ-cells into insulin producers. Nature 514: 503-507, 2014.

NEW INSIGHTS FROM TYPE 1 DIABETES GENETICS

Gene Affecting Risk for Type 1 Diabetes Involved in Maintaining Healthy "Power Plants" in Insulin-producing Cells: Researchers have found that a gene known to affect risk for type 1 diabetes encodes a protein involved in quality control of mitochondria—the cell's "power plants." Found in cells throughout the body, mitochondria are specialized metabolic structures that have the critical job of converting the energy that is ingested (sugars and fats, for example) into a chemical form that is more readily usable by cells. Over time, mitochondria may develop problems, and require recycling and replacement to keep cells going strong. A protein called Parkin initiates this multi-step recycling process, which marks the mitochondria for death and eventually results in their destruction. Working with mice, the researchers found that *Clec16a*—a gene linked to risk for type 1 diabetes in human studies—encodes a protein involved in targeting Parkin for destruction. They found that reducing the amount of Clec16a protein resulted in an increase in Parkin levels, causing mitochondrial recycling to be initiated too frequently. Interestingly, the researchers found that pancreatic islets lacking Clec16a had more mitochondria, not fewer, suggesting that Clec16a not only acts as a check on mitochondrial recycling, but also is critically involved in completing mitochondrial destruction once the process is initiated. Further, although insulin-producing β (beta) cells that lack Clec16a have more mitochondria, they

are less able to process energy for the cell and produce less insulin in response to rising blood glucose (sugar) than normal β cells do. These data suggest that initiation of the recycling process at least partially incapacitates the mitochondria and weakens the insulin response. Notably, people with a common mutation of *CLEC16a* that is linked to type 1 diabetes also have lower cellular levels of the Clec16a protein and poorer insulin response than people with other variants of the gene, suggesting the protein's role in humans is similar to its role in mice. Although it is uncertain precisely how a defect in mitochondrial recycling might lead to type 1 diabetes, the researchers found that mouse β cells lacking Clec16a showed signs of cellular stress that might make them more susceptible to a disease-initiating autoimmune attack. Further research is needed to verify the role of Clec16a in maintaining β cell health, and to determine whether modulating the mitochondrial recycling program might help prevent the disease.

Soleimanpour SA, Gupta A, Bakay M,...Stoffers DA. The diabetes susceptibility gene Clec16a *regulates mitophagy.* Cell *157: 1577-1590, 2014.*

Study of Children at Genetic Risk of Developing Type 1 Diabetes Sheds New Light on Celiac Disease: A study found that more than one quarter of children with two copies of a specific genetic variant develop an early sign of celiac disease, called celiac disease autoimmunity (CDA), by age 5. Results also showed that children's risk of developing CDA was different depending on where they lived. These results are from The Environmental Determinants of Diabetes in the Young (TEDDY) study, an international study that is investigating both celiac disease and type 1 diabetes, because both are autoimmune diseases sharing some of the same genetic risk factors. Although the primary aim of TEDDY is to understand what environmental factors trigger or protect against type 1 diabetes in children, researchers are able to mine the data for insights into celiac disease. Celiac disease stems from an immune reaction to gluten, a protein found in wheat, rye, and barley. Over time, celiac disease can damage the small intestine and cause other health problems. People with celiac disease or CDA must follow a gluten-free diet to prevent or reduce this damage, so it is important—but currently challenging—to identify people early in the course of the disease so that they can implement dietary changes before intestinal damage occurs.

TEDDY researchers followed 6,403 newborns with one of two high-risk genetic variants (*HLA-DR3-DQ2* or *HLA-DR4-DQ8*) that are known to increase susceptibility to celiac disease to see who would develop celiac disease or CDA. Overall, 12 percent of the children had CDA at 5 years of age. However, youth with two copies of *HLA-DR3-DQ2* had the highest likelihood of disease development by age 5. Of this group, 26 percent developed CDA by age 5, and 11 percent developed celiac disease. The study also found that girls were at greater risk than boys for CDA. Additionally, Swedish children had higher rates of CDA and celiac disease than participants in the United States, Finland, and Germany, even when matched for the same genetic risk. In fact, Swedish children had nearly double the risk of CDA compared to American children with the same genetic risk variants; the extra risk faced by the Swedish children may come from environmental or other factors. These results could help inform future recommendations for celiac disease screening in young children and pave the way to early personalized prevention and treatment approaches based on genetic risk. They also suggest the need for further research to understand the environmental factors that influence the development of celiac disease in those who are genetically susceptible, which the TEDDY study is also addressing.

Liu E, Lee H-S, Aronsson CA,...Agardh D; TEDDY Study Group. Risk of pediatric celiac disease according to HLA haplotype and country. N Engl J Med *371: 42-49, 2014.*

METABOLIC REGULATORS OF HEALTH AND DISEASE

Understanding How Nerve Cells Detect and Respond to Available Glucose: Researchers identified cellular factors that monitor the availability of glucose (sugar), the primary nutrient source for nerve cells (neurons), and enable these cells to use these sources to generate energy. Fuel sources are used to make

energy by specialized structures in the cell called mitochondria. Mitochondria are dynamic and move around within neurons to generate energy in response to local energy needs in these elongated, complex cells. Therefore, the mechanisms that sense energy status and regulate mitochondrial movement are important for cell function. Thus, researchers were interested in understanding those cellular mechanisms.

Glucose is a key fuel source for neurons, but these long cells can traverse considerable distances through the brain, and glucose concentrations are unlikely to be the same everywhere along the nerve cell. How do the energy-generating mitochondria, which migrate throughout the neuron, know to pause at the regions of high nutrients where they are most needed? The researchers hypothesized that mitochondrial movement may be regulated by local glucose levels outside of the cell. To test this hypothesis, they examined mitochondrial movement in rat neurons grown in laboratory culture in either low or high glucose levels. They found that mitochondrial movement decreased when glucose levels were high. The researchers then examined the mechanisms by which cells sensed glucose to regulate mitochondrial movement. They zeroed in on a protein called O-GlcNAc Transferase (OGT). OGT catalyzes the addition of special types of activated glucose molecules to proteins. OGT's activity depends on the availability of glucose—making it a "metabolic sensor" for glucose. The scientists found that inducing high levels of OGT experimentally in cultured neurons decreased mitochondrial movement, mimicking the effect seen with high glucose levels and suggesting that glucose may be working through OGT to reduce mitochondrial movement.

Next, to understand how OGT may be exerting these effects, the researchers studied another protein called Milton. Milton binds to a protein on mitochondria, as well as to proteins on intracellular structures (microtubules) that are involved in transporting mitochondria and other organelles around cells. By way of analogy, Milton connects the train car (mitochondria) to the wheels on the track (proteins on microtubules). Through a series of cell culture experiments, the scientists discovered that, in the presence of glucose, OGT was activated and added sugar molecules to Milton, and this modification was necessary to decrease mitochondrial movement. These results suggest that, in the presence of glucose, OGT is activated and modifies Milton, and modified Milton serves as a "brake" to keep the mitochondria in place so they can metabolize the available glucose. In contrast, when glucose is scarce, OGT is not activated, Milton is unmodified, there is no brake, and mitochondria move to another part of the cell.

This research shows that mitochondrial movement is regulated by glucose through OGT modification of Milton. It also suggests that OGT is a key nutrient sensor for neurons and promotes local energy production near where fuel is abundant. Although most of the experiments were conducted in neurons, the proteins are found in other cell types, suggesting that glucose, through OGT, may be a global regulator of mitochondrial movement.

Pekkurnaz G, Trinidad JC, Wang X, Kong D, and Schwarz TL. Glucose regulates mitochondrial motility via *Milton modification by O-GlcNAc transferase. Cell 158: 54-68, 2014.*

FGF1 as a Possible Novel Therapeutic for Type 2 Diabetes: Scientists demonstrated that a protein called FGF1 has potential as a new therapeutic for type 2 diabetes. In people with type 2 diabetes, cells in muscle, fat, and liver tissue lose their ability to respond to insulin, a hormone necessary for the body to use glucose (sugar). This condition is referred to as "insulin resistance" and is often the first step in development of type 2 diabetes. One approach to treating type 2 diabetes is to develop strategies to improve the body's sensitivity to insulin. A class of type 2 diabetes medications—thiazolidinediones—act as insulin sensitizers; however, they also have significant side effects like weight gain, bone loss, and increased risk for heart failure. Scientists, therefore, continue to search for agents that improve insulin sensitivity without leading to unwanted side effects.

A group of researchers hypothesized that FGF1 had a role in regulating blood glucose levels based on previous results linking FGF1 deficiency to

diet-induced insulin resistance in rodent models. FGF1 normally acts locally; it does not circulate throughout the body. To evaluate the potential of FGF1 to modulate glucose levels when distributed more broadly in the body, the researchers injected FGF1 in male mice that had insulin resistance resulting from genetic mutations or from diet-induced obesity, and measured the effect of this treatment on blood glucose levels. They found that a single administration of FGF1 normalized blood glucose levels within 18 to 24 hours, and that chronic administration of FGF1 every other day for 35 days resulted in a sustained reduction in blood glucose levels.

Administration of FGF1 did not affect blood glucose levels in normal insulin-sensitive mice, and did not cause insulin levels to rise, suggesting that FGF1's effects were not mediated by increasing insulin production in the body. Further research demonstrated that insulin was required for FGF1 to exert its effects on glucose levels. These results indicated that, under these circumstances, FGF1 does not replace insulin, but instead acts in concert with insulin to regulate blood glucose. Additional experiments suggested that FGF1 acted as an insulin sensitizer, as FGF1 increased the mice's responsiveness to insulin.

Importantly, FGF1-treated mice did not exhibit side effects associated with thiazolidinediones, such as weight gain or reduced bone density. However, FGF1 can induce cell proliferation, a property raising safety concerns that could limit its usefulness as a therapy. To address this potential problem, the researchers tested a modified version of FGF1 that did not stimulate cell proliferation. The modified version retained the ability of FGF1 to improve insulin sensitivity, demonstrating that FGF1's action to reduce glucose can be separated from its proliferative activity. These promising results indicate that FGF1 may have potential as a new therapeutic for type 2 diabetes, if similar results are observed in human studies.

Suh JM, Jonker JW, Ahmadian M,...Evans RM. Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer. Nature 513: 436-439, 2014.

RESEARCH ON CYSTIC FIBROSIS AND OTHER RARE DISEASES

Understanding Why a Promising Therapeutic Approach for Cystic Fibrosis Is Not Working as Hoped May Lead to Improved Treatment Options: New research helps explain why a therapeutic approach currently being tested for cystic fibrosis (CF) is providing little therapeutic benefit, but also suggests alternative approaches that might be more successful. CF is caused by mutations in the *CFTR* gene. Many such disease-causing mutations have been identified. Some mutations yield a version of the CFTR protein that is present in normal amounts and at the right location in the cell, but unable to do its job: letting chloride ions into or out of the cell.

Recently, a medication called VX-770 (ivacaftor; marketed as Kalydeco™) was approved for use by the U.S. Food and Drug Administration. This drug is able to open the chloride channel in people with *CFTR* mutations that produce reasonably stable but inactive CFTR protein, an enormous therapeutic advance for people with this type of mutation. Other *CFTR* mutations, however, make the CFTR protein unstable, causing cells to degrade it before it can fulfill its cellular role. The most common CF-causing mutation, called *ΔF508*, does both of these things: it destabilizes the protein and also inactivates its chloride channel function. Thus, for the majority of people with CF, VX-770 alone is inadequate, and another drug is needed to stabilize the CFTR protein. Researchers previously found that treating cells from people with *ΔF508* with either of two promising CFTR-stabilizing medications led to a meaningful increase in the amount of CFTR protein reaching the cell surface, where it is needed. Subsequent treatment of the cells with VX-770 led to a measurable boost in chloride transport, raising hopes that "combination therapy" with VX-770 and one or the other of the stabilizing medicines would yield clinical benefits for people with *ΔF508*. Surprisingly, however, initial results from clinical trials testing this approach have been disappointing.

In new studies from two different research groups, scientists sought to understand why combination

therapy seems so much less effective in clinical trials than it does in cells grown in the laboratory. The two groups both noted that the preliminary cell experiments involved ongoing treatment with the CFTR-stabilizing medications, followed by a shorter-duration treatment with VX-770. For this reason, they repeated the cell-based experiment, but administered VX-770 continuously, to more closely parallel its administration in the clinical trials. Both groups found that, in cells expressing the *ΔF508* version of the CFTR protein, chronic VX-770 administration had the effect of further destabilizing the protein—effectively undoing the beneficial action of the candidate stabilizing drugs. One of the research groups noted that this finding suggests it might be beneficial to fine-tune dosing of VX-770 and candidate stabilizing drugs to optimize benefit for people with the *ΔF508* mutation. The other group tested a panel of other candidate channel-opening medications in cells with the mutation, and found one called P5 that did not exhibit the same destabilizing effect as VX-770. P5 is still in pre-clinical stages of development, so it is not yet clear whether it would be safe and effective in people with *ΔF508*. Even if not, however, the observation suggests it might be possible to find a drug combination that provides sustained benefit for most people with CF.

Cholon DM, Quinney NL, Fulcher ML,...Gentzsch M. Potentiator ivacaftor abrogates pharmacological correction of ΔF508 *CFTR in cystic fibrosis. Sci Transl Med 6: 246ra96, 2014.*

Veit G, Avramescu RG, Perdomo D,...Lukacs GL. Some gating potentiators, including VX-770, diminish ΔF508-CFTR *functional expression. Sci Transl Med 6: 246ra97, 2014.*

Study of a Rare Genetic Disorder of Metabolism Leads to a Promising Therapeutic Approach: A recent analysis has clarified understanding of the metabolic disorder glycogenesis type XIV, and found that dietary supplementation with the sugar galactose may be a practical approach to alleviate some of the health effects of the disease, which can damage the heart, liver, and other organs. People with glycogenesis type XIV are unable to make phosphoglucomutase 1, an enzyme that helps supply some of the specific carbohydrate (sugar) "building blocks" used to make glycoproteins, an important group of molecules with diverse roles in the body. Phosphoglucomutase 1 is also involved in the storage of carbohydrates in liver and muscle, as well as in the utilization of that stored energy. The study began with a pair of brothers with an unusual combination of symptoms: muscle weakness, liver disease, short stature, cleft palate, and recurring hypoglycemia (low blood glucose). Genetic testing revealed that both boys had mutations in each of their two copies of the gene for phosphoglucomutase 1, with the effect that they produced none of the enzyme. The researchers identified 17 more individuals who were similarly unable to produce active phosphoglucomutase 1 and experienced a similar (though somewhat variable) constellation of symptoms.

To investigate how the lack of phosphoglucomutase 1 might cause the signs and symptoms of glycogenesis type XIV, the researchers compared the array of sugars available for making glycoproteins in cells from people with and without the enzyme. They found that people without the enzyme are unable to make significant amounts of a compound called UDP-galactose. Although the body normally produces UDP-galactose *via* a process utilizing phosphoglucomutase 1, an alternative path exists whereby the body can make UDP-galactose from the naturally occurring sugar, galactose. Galactose by itself is not normally a significant part of a person's diet, although it is bonded to another sugar, glucose, in the milk sugar, lactose. The scientists found that adding a small amount of galactose to the diet of six of the people lacking phosphoglucomutase 1 significantly improved their ability to make glycoproteins, helped improve heart function, and alleviated some of the other impacts of the disease. Supplemental lactose, on the other hand, had no effect. In addition, the researchers developed a blood test that may help diagnose glycogenesis type XIV. Long-term studies will be needed to determine whether galactose is a safe and effective treatment for people with this rare genetic disease.

Tegtmeyer LC, Rust S, van Scherpenzeel M,...Marquardt T. Multiple phenotypes in phosphoglucomutase 1 deficiency. N Engl J Med 370: 533-542, 2014.

The National Diabetes Education Program Provides Resources To Support Improved Care for People with or At Risk for Diabetes

The National Diabetes Education Program (NDEP)—a joint effort of the NIH and the Centers for Disease Control and Prevention—shares model programs and resources to help health care providers and community-based organizations support their constituents to develop and sustain healthy lifestyles to delay or prevent type 2 diabetes, or effectively manage diabetes and improve outcomes.

Established in 1997, the NDEP is a federally funded program that includes over 200 partners at the federal, state, and local levels. NDEP partners work together to improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes.

Support for Behavior Change

Working with its partners, the NDEP developed the Diabetes HealthSense website to meet the need for resources and tools to promote behavior change and to address the psychosocial and lifestyle-change challenges associated with diabetes self-management. Diabetes HealthSense provides health care professionals and their patients with easy access to resources for making lifestyle changes and coping with stress and emotional health issues. Health care professionals can gain access to patient tools as well as a complete library of review articles, landmark studies, and meta-analyses to facilitate behavior change in clinical practice settings. Resources have been reviewed by leading independent experts on psychosocial issues with specific expertise on how to make and sustain lifestyle changes. This Web resource can be found at *www.YourDiabetesInfo.org/HealthSense*

New Guiding Principles

A newly published set of 10 guiding principles highlights areas of agreement for diabetes care that could be clinically useful in diabetes management and prevention. Presented by the NDEP, *Guiding Principles for the Care of People With or at Risk for Diabetes* is aimed at assisting with identification and management of the disease, self-management support for patients, physical activity, and blood glucose (sugar) control, among other topics. More than a dozen federal agencies and professional organizations support the document, which can be found at *http://ndep.nih.gov/hcp-businesses-and-schools/guiding-principles/*

To find more resources from the NDEP, please visit *www.YourDiabetesInfo.org*

(Adapted from a piece originally published in the fall 2014 NIDDK Director's Update.)

Accelerating Medicines Partnership

The NIH, 10 biopharmaceutical companies, the U.S. Food and Drug Administration, and several non-profit organizations have designed an unprecedented new partnership. Managed through the Foundation for the NIH (FNIH), the Accelerating Medicines Partnership (AMP) seeks to identify and validate the most promising biological targets of disease for new diagnostic and drug development. The partners have designed a milestone-driven research plan to tackle this challenge for type 2 diabetes, as well as for Alzheimer's disease and the autoimmune disorders rheumatoid arthritis and systemic lupus erythematosus (lupus). A key feature of this public-private partnership that makes it unique is that AMP data will be considered precompetitive and made publicly accessible to the broad biomedical community for further research.

The AMP Approach to Finding New Type 2 Diabetes Therapies

The AMP type 2 diabetes partnership will be a 5-year initiative, from mid-2014 through mid-2019. The partnership steering committee will ensure substantial scientific and logistical interaction among the partners to catalyze diabetes drug development by taking advantage of a major existing asset in the field of type 2 diabetes research: the tremendous volume of genetic data on the disease in diverse populations—made possible primarily through NIH-supported research—which is unmatched in most other diseases. Much of the information on gene variation can be linked to clinical information and knowledge about how and in what parts of the body the genes function, making the combined data a potentially rich resource for research aimed at better understanding and treating this complex disease. The AMP plans to leverage that great strength, using and supplementing the genetic data to identify and validate novel molecules and pathways as targets for therapeutic development.

To speed analysis, researchers will assemble a "Knowledge Portal"—a database of gene sequences, known variants, functions, regulatory information, and associated clinical data from studies on type 2 diabetes and its cardiac and renal complications, involving 100,000 to 150,000 individuals. The data set and analytical tools will be accessible to academic and industry researchers to identify and validate changes in DNA that spur the onset of diabetes, alter disease severity, speed or slow disease progression, or have a protective effect. The NIDDK-led Multiethnic Study of Type 2 Diabetes Genes Consortium (T2D-GENES) is independently developing and testing a database and Web utility that may serve as a prototype for the AMP Knowledge Portal. This resource will bring together data in a way that is useful not only to geneticists, but also to drug discoverers and investigators in many other specialties of type 2 diabetes research.

Generating New Genomic Data

As the Knowledge Portal is being mined and analyzed, the partnership will seek to fill in data gaps and

investigate targets of particular interest by sequencing key genes in specific populations, hoping to find, for example, a genetic variant that occurs in few individuals but has a significant effect on disease risk or progression. Such discoveries can provide clues about the biological processes underlying the disease and uncover possible therapeutic targets.

A case study in how this might work comes from recent discoveries about the gene *SLC30A8*, which encodes the protein ZnT8. The gene first came to the attention of diabetes researchers when they discovered that common *SLC30A8* genetic variants cause a modest increase in risk for type 2 diabetes. New research recently identified much rarer mutations in the gene that appear to have the opposite effect, providing significant protection from the disease. These rare mutations inactivate one copy of the gene, effectively cutting the amount of ZnT8 a person produces in half. This finding suggests a potential strategy for pharmacologic prevention or treatment of type 2 diabetes might target reducing the amount of this protein.

By combining resources to investigate many such genetic opportunities, the AMP partners hope to open a new era of treatment and prevention for people with or at risk for type 2 diabetes. For more information on this program, please see:
www.nih.gov/science/amp/type2diabetes.htm

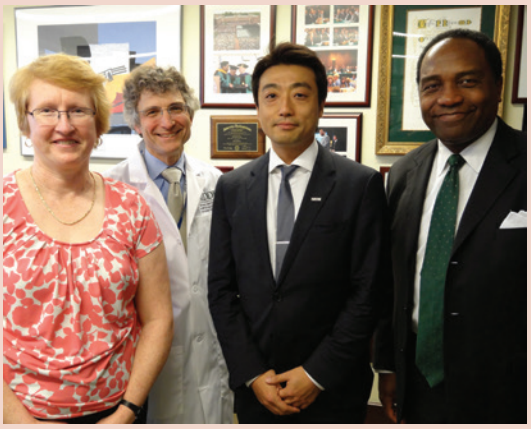
Dr. Shingo Kajimura Receives Prestigious Presidential Award

NIDDK-supported scientist Dr. Shingo Kajimura has received the Presidential Early Career Award for Scientists and Engineers (PECASE).

The PECASE is awarded annually to scientists and engineers who, while early in their research careers, have demonstrated the pursuit of innovative research and outstanding scientific leadership. Dr. Kajimura was honored for his important contributions to understanding the development of brown adipose tissue, also known as brown fat. Unlike white adipose tissue, which is used by the body to store excess energy, brown fat burns energy to produce heat and help protect the body from cold exposure. Because brown fat is capable of burning many calories quickly, it is hoped that learning how to regulate its development and activity may one day become therapeutically valuable for the prevention and treatment of obesity and related metabolic conditions.

Elucidating the Path Toward Brown Fat Development in Humans

Adults vary considerably in the amount of brown fat they possess, although people who are thinner tend to have more than individuals who are overweight or obese. Prolonged and repeated exposure to cold is known to help trigger development of brown fat in adults, but there is great interest in better understanding the way this occurs, to help people produce this calorie-burning type of cell without enduring such discomfort. Brown adipose cells are known to form from precursor cells that also have potential to develop into skeletal muscle. Dr. Kajimura's work helped establish that precursor cells become brown fat if they are making a protein called PRDM16, while those that do not make this protein become skeletal muscle. Recently, Dr. Kajimura and colleagues identified another key piece of the puzzle, by studying brown fat development in mice. They showed that PRDM16 must work in concert with a different protein, called EHMT1, to drive the precursor cells to become brown fat cells. Further, they found that a lack of EHMT1 in male mice led to a severe loss of potential to form brown fat cells, and to obesity. Rare mutations that reduce EHMT1 in humans also result in obesity, among other consequences, although it is currently unknown whether humans lacking the protein also have a diminished capacity to produce brown fat.



From left, Dr. Carol Haft, NIDDK program director for adipocyte biology; NIDDK Deputy Director Dr. Gregory Germino; Dr. Shingo Kajimura; and NIDDK Director Dr. Griffin Rodgers. The group met on the NIH campus during Dr. Kajimura's trip to Washington, D.C., to accept his award from the White House. (*Photo Credit: Jen Rymaruk*)

By contributing to the understanding of how the body controls formation of brown fat, Dr. Kajimura's research may lead to the development of therapeutic approaches to stimulate human brown fat production, potentially helping people to maintain a healthier weight and metabolism.

The PECASE awards support the continued professional development of awardees, promote careers and foster innovation in science and technology, and recognize the scientific missions of participating agencies. A list of NIH scientists who have received this prestigious award is available at *www.grants.nih.gov/grants/policy/pecase.htm*

STORY OF DISCOVERY

Leptin as a Treatment for Generalized Lipodystrophy: A Translational Success Story

In 1949, researchers identified a new mouse model that was extremely obese. Little did they know that research on that obese mouse would lead—65 years later—to an approved medical treatment for people who lack fat tissue altogether.

But, that is exactly what happened, after many decades of research that included the discovery of a hormone called leptin. The translational success was a result of collaborations among many scientists, including NIDDK-supported scientists at universities, scientists in the NIDDK Intramural Research Program, industry researchers, and many others. This story demonstrates how exciting discoveries in the laboratory provide the foundation for improving the health of people.

The Obese Mouse and the Discovery of Leptin

Scientists who identified the obese mouse model in 1949 called the unknown gene causing the obesity "*ob*." By the 1980s, the identity of the *ob* gene was still a mystery, but it was becoming more and more apparent that research on genetic contributors to obesity was critically important to pursue. Therefore, the NIDDK sought to support research to identify obesity-related genes in rodents, including the *ob* gene. The Institute sponsored a workshop on this topic and developed an initiative to solicit research applications.

In 1989, the NIDDK awarded a grant to Dr. Jeffrey Friedman through this initiative. Dr. Friedman's subsequent pioneering research led to the 1994 discovery of the mouse *ob* gene. The hormone produced by this gene was named "leptin," a term that derives from a Greek word meaning thin. Because the *ob* mutant mouse was obese, the scientists realized that the normal *ob* gene—and the hormone it encodes—must contribute to leanness.

The landmark discovery of leptin unleashed a wave of new research advances in fat biology and metabolism. Researchers found that leptin is secreted by fat cells and released in proportion to the amount of fat. These observations drastically altered the prevailing view of normal fat tissue as simply a metabolically passive "fat storehouse." Research fueled by this 1994 discovery also led to the identification of a number of other substances that, like leptin, are secreted by fat cells and influence appetite and metabolism.

Studies demonstrated that obese animals deficient in leptin, including mice carrying the mutant form of the *ob* gene, lost weight when given the hormone. Therefore, researchers postulated that leptin treatment might also be useful for human obesity. There are, in fact, very rare instances of complete deficiency of leptin in humans that result in morbid obesity from infancy. Leptin treatment in these individuals caused substantial weight loss, providing hope for improved quality of life and longevity.

Unfortunately, in clinical studies done at that time, leptin administration was not effective in treating the vast majority of cases of human obesity, which are not due to leptin deficiency. In most cases, obesity results from a complex interaction among an individual's

genes and the environment. Obese individuals, in fact, usually have very high levels of leptin, probably a consequence of the many fat cells secreting it. The inability of the high levels of leptin to decrease body weight suggests that the more common forms of obesity are associated with a resistance to leptin's actions. Although these results were disappointing, scientists did not give up in their quest to use this new knowledge to benefit people.

Testing Leptin as a Treatment for Lipodystrophy

Scientists in the NIDDK's Intramural Research Program had broad experience with respect to studying people with various forms of insulin resistance. Using this experience and knowledge, they identified a patient population—people with lipodystrophy—who could potentially benefit from leptin treatment.

Lipodystrophy is actually a group of disorders with disparate origins but with a common set of metabolic consequences. Lipodystrophy can either be genetic or acquired, and can be generalized (near total lack of fat) or partial (fat loss in certain parts of the body). While lipodystrophy is characterized by the loss of fatty tissue in certain areas of the body, tissues such as liver and muscle exhibit significant abnormal accumulation of fat, which impairs metabolic activity. People with the disorder also exhibit resistance to the effects of insulin and are thus at high risk of developing diabetes. They may also have a range of lipid abnormalities.

Treatment of lipodystrophy has included the administration of insulin, oral hypoglycemic (blood glucose [sugar]-lowering) agents, and lipid-lowering drugs. Even with treatment, people with lipodystrophy continue to have severely high levels of triglycerides, leading to recurrent attacks of acute inflammation of the pancreas; severe problems controlling blood glucose levels, posing risks of developing diabetic complications; and fat accumulation in the liver, which can result in cirrhosis and liver failure.

Because many people with lipodystrophy have low leptin levels due to the lack of fat cells that produce the hormone, and because research had demonstrated beneficial effects of leptin on insulin sensitivity and fat metabolism in a number of tissues, researchers in the NIDDK Intramural Research Program and their collaborators, including major collaborators at the University of Texas Southwestern and Yale University, investigated whether leptin treatment could ameliorate conditions associated with lipodystrophy.

Results from two small clinical studies testing this hypothesis were published in 2002. The studies showed that short-term leptin therapy (3 to 8 months) had dramatic benefits in individuals with lipodystrophy. In one study of females with different forms of lipodystrophy, most of whom also had diabetes, leptin therapy improved blood glucose levels, lowered triglyceride levels, and decreased liver fat content. In another study, leptin therapy markedly improved insulin sensitivity, lowered lipid levels, and decreased liver fat content in individuals with severe lipodystrophy who also had poorly controlled diabetes. Participants in these studies were able to reduce or discontinue their diabetes medications.

Seeing such dramatic results, researchers next examined the effect of longer-term leptin therapy. In results published in 2005, the researchers found that in 15 people with severe forms of lipodystrophy and poorly controlled diabetes, 12 months of leptin treatment led to improved blood glucose and blood lipid levels, and decreased fat in their livers. Participants also reported a dramatic reduction in their appetite, which led to moderate reductions in their

weight. In addition, they were able to discontinue or reduce their diabetes medications. In 2010, the scientists reported similarly remarkable results in 35 participants treated with leptin for 12 months.

The scientists also examined the effect of leptin on other metabolic abnormalities associated with lipodystrophy. For example, females often have irregular or absent menstrual cycles; leptin treatment was found to correct that condition. Leptin treatment was also highly effective in treating people with lipodystrophy and nonalcoholic steatohepatitis (NASH), a progressive metabolic liver disease. In a study of 25 people, researchers found that a surprisingly high number had some form of kidney disease; leptin treatment was found to improve their kidney function. Thus, leptin corrected a broad range of metabolic defects associated with lipodystrophy.

Because lipodystrophy is a chronic condition, it was important for the researchers to study whether leptin treatment was safe and effective to use as a long-term treatment. In 2011, they reported the results of a study of 55 people with lipodystrophy who were treated with leptin for 3 years: the participants had robust and sustained improvements in their blood glucose and blood lipid levels, and also had improvements in markers of liver function, a sign that the excess fat in their livers had likely diminished. Importantly, there were few adverse reactions to leptin during the study. Together, these data suggest that leptin is a safe and highly effective treatment for people with lipodystrophy.

Leptin Is Approved as a Treatment for People with Generalized Lipodystrophy

As a result of the clinical studies described above, in 2010, the industry collaborator that provided the leptin used in the studies—Amylin Pharmaceuticals/Bristol-Myers Squibb/AstraZeneca—began the process to submit a "biological license application" to the U.S. Food and Drug Administration (FDA) seeking approval to use leptin (marketed as Myalept™) as a treatment for people with lipodystrophy; the application was completed in 2012. The primary data used in the application were directly from the NIDDK's clinical studies.

In February 2014, the FDA made the exciting announcement that it approved Myalept™ for treating people with generalized lipodystrophy—whether genetic or acquired—in addition to following a healthful diet. Of note, leptin treatment helps people with lipodystrophy follow a healthful diet. Without leptin, they are always hungry; leptin treatment dramatically reduces their appetite and thus also decreases their food intake.

Leptin is the first approved therapy that is indicated for people with generalized lipodystrophy. People may still need to take conventional medicines (*e.g.*, lipid-lowering drugs or insulin), but required dosages of those medicines are markedly lower while taking leptin. In particular, people are often able to discontinue insulin use.

The FDA approval of leptin represents a much-needed treatment for people with generalized lipodystrophy—a rare and life-threatening disorder for which available therapies were only partially effective and did not address the underlying cause of the metabolic abnormalities, leptin deficiency.

A Team Effort Leads to a Research Success Story

The clinical studies testing leptin therapy for lipodystrophy conducted by the NIDDK Intramural

Research Program—and used as the primary scientific basis for FDA approval—required numerous collaborators and spawned new collaborations. Leading this effort was Dr. Phillip Gorden, a former NIDDK Director who returned to the laboratory to continue his research. Because the leptin used in the research was manufactured by industry, the Intramural Research Program and the NIDDK Technology Advancement Office worked with industry to obtain the leptin needed for the studies. In addition, because lipodystrophy affects the liver and kidneys, scientists in the Intramural Research Program with expertise studying those organs were valuable contributors to the studies. Furthermore, collaborators external to the NIDDK have studied the underpinnings of different forms of genetic lipodystrophy; several genes have now been identified. Finally, many of the study participants were evaluated and treated at the NIDDK's Metabolic Clinical Research Unit, a facility in the NIH Clinical Center that enables scientists to make precise metabolic measurements. It was only through the contributions of all of these collaborators that this translational success story came to fruition.

Looking to the Future

As described in this story, knowledge gained from studying a common condition, obesity, led to the discovery of leptin and a treatment for a very rare disease, generalized lipodystrophy. Scientists are now coming full circle by building on the successful clinical studies with leptin in lipodystrophy and applying that knowledge to research on common diseases. For example, by studying women with lipodystrophy, scientists in the NIDDK Intramural Research Program are also gaining insights into a more common condition: polycystic ovarian syndrome (PCOS). PCOS is a set of symptoms that results from a hormonal imbalance; it affects females of childbearing age and is the most common cause of anovulatory (absence of ovulation) infertility. Women with lipodystrophy have features of PCOS, which are improved by leptin therapy. This observation suggests that knowledge gained by studying women with lipodystrophy may provide understanding of the more complex and common PCOS and shed light on improved ways to treat it.

NIDDK-supported scientists are also gaining important insights into leptin's biological functions, which are informing future research. For example, NIDDK-supported extramural researchers found that after people lost 10 percent of their body weight, their leptin levels and metabolic rate decreased, resulting in a metabolic state that favors weight regain. Researchers discovered that leptin replacement after weight loss increases people's metabolic rate to the pre-weight loss level. Although it is not yet known whether giving people leptin could help maintain weight loss, the findings suggest the need for future research to develop novel therapies to support weight loss maintenance.

Other NIDDK-supported researchers are exploring leptin's use in treating other diseases and disorders. For instance, NIDDK-supported extramural researchers found that leptin treatment improved the health of women with a condition called hypothalamic amenorrhea (absence of a menstrual cycle due to excessive exercise or stress, or inadequate food intake), which can result in infertility and bone loss. In women with this condition, leptin treatment restored menses and ovulation, independent of weight gain. In addition, researchers in the NIDDK Intramural Research Program studied people with a rare genetic syndrome caused by mutations in the gene encoding the insulin receptor, which results in extreme insulin

resistance; people with this syndrome have a very difficult time controlling their blood glucose levels. In a small study, the researchers found that leptin treatment improved patients' blood glucose levels. These studies have identified other populations who may possibly benefit from leptin treatment.

Through future research, it is also important to identify safe and effective treatments for people with other forms of lipodystrophy, including rare forms of partial lipodystrophy, as well as a more common form of lipodystrophy that is acquired from taking certain types of medications for human immunodeficiency virus (HIV). While leptin was approved for a rare form of lipodystrophy, partial forms of the disorder are more common and additional research is needed to identify others who might benefit. Thus, future research is needed to identify therapies to improve the health of all people with lipodystrophy.

Conclusion

The FDA approval of leptin for generalized lipodystrophy is a culmination of decades of research—NIDDK-supported basic research that led to the discovery of leptin, as well as clinical research conducted by scientists in the NIDDK Intramural Research Program and their collaborators testing leptin in people. People with lipodystrophy were not originally envisioned as a group who would benefit from leptin treatment, as leptin was first thought to be a promising treatment for common forms of obesity. But, because of the dedication of numerous scientists and clinical trial volunteers, people with generalized lipodystrophy have a new FDA-approved treatment. It is a translational success story representing the ultimate goal of NIDDK-supported research—to improve people's health and quality of life.

PATIENT PROFILE

Edward Augustin

A Life with Type 1 Diabetes Turned Around by Islet Transplantation

Ed Augustin and his daughter Jill

December 4, 2011, 7:04 am. It's a date that Edward (Ed) Augustin won't forget. That morning, Ed woke up at the University of Illinois Medical Center in Chicago a changed man. For the first time he could remember, Ed didn't have to worry about his type 1 diabetes. He had just received a transplant of insulin-producing islet cells. "I'm ecstatic," he exclaims, "I'm the luckiest guy in the whole universe. There are just not words that I can say to tell you how happy I am."

Ed wasn't always so happy. When he was a young child, he explains, "My mom noticed that something was wrong. I was thirsty and going to the bathroom all of the time. Finally, one day, she said we're going to go get a blood test." He was diagnosed with type 1 diabetes when he was only 5 years old. Ed spent a week in the hospital learning about his new life of diets and insulin shots. "It was horrible," he recalls. "The only time I've ever seen my dad cry was when they told me you've got to go to the hospital."

Type 1 diabetes is an autoimmune disease in which a person's immune system destroys the cells that make insulin. These cells are found in the pancreas in clusters called islets. People with the disease must carefully monitor their blood sugar (glucose) levels and administer insulin. Without insulin, the cells of the body starve, while the excess sugar in the blood can, over time, lead to devastating complications of the eyes, kidneys, nerves, and heart. Too much insulin, however, can cause blood sugar levels to fall dangerously low, a condition called hypoglycemia, which can lead to confusion, difficulty in awakening, loss of consciousness, seizures, and death. It is very difficult for people with type 1 diabetes to achieve a balance between too much sugar in the blood and too little; it was even more difficult when Ed was diagnosed over 50 years ago, before the development of advanced medical technologies.

Life with Type 1 Diabetes

In 1961, life for people with type 1 diabetes was different from the way it is now. Ed's parents were told he would only live for another 5 years. Fortunately, he was too young to understand—and he defied those odds. He went on a strict, measured diet. "Never again was I to have sugar. When I went into the hospital for the first time, my mom bought me a fudge sundae and said: 'This is your last fudge sundae.'"

PATIENT PROFILE

Ed's sugar levels were measured with urine tests, a procedure that, to this day, has been etched in his memory because he didn't like doing them.

His family was vigilant in administering his shots of insulin, which at that time were given in glass syringes with insulin that had to be kept cold. "Mom watched me like a hawk," he remembers. His parents also tried to teach him to give himself insulin shots, but "I didn't want to learn because then I'd have to give myself a shot, and I didn't want to take the shot," he shares. So, Ed's parents taught his siblings how to give insulin shots. "They taught my sister, and she'd give me a shot. They taught my brother, and he nailed me with a shot. And he liked it," laughs Ed, "so I didn't like it when he did it."

When Ed had a hypoglycemic reaction, he'd lose control. He couldn't think straight, couldn't talk, couldn't put words together. He would be completely disoriented.

Despite his family's watchful care, Ed's diabetes was particularly difficult to control, meaning that, even with his strict diet and insulin administration, Ed's blood sugar levels varied wildly between very high and very low. Ed had hypoglycemic reactions, also known as "hypoglycemic episodes," when his blood sugar got dangerously low. When Ed had a hypoglycemic reaction, he'd lose control. He couldn't think straight, couldn't talk, couldn't put words together. He would be completely disoriented.

These episodes were especially difficult to manage when he wasn't at home. As a child, he'd "know I was going down for the count because I'd sweat or see double." But when he was playing in the schoolyard and began experiencing these symptoms, he'd need to eat something to raise his blood sugar levels, even sweets that weren't part of his normal diet. "I'd just hope I was close to a candy bar. If I was close to a candy bar, that was good. Sometimes, you had to get on your bike and go ride home to get the candy bar," he remembers. Ed was the only kid with type 1 diabetes in his school and neighborhood, and he never told his classmates and friends what was going on. "You didn't tell any of your friends because they'd think you're weird," he shares. "No one could understand how a kid can fall to the ground and not be able to run with the football anymore."

Then, when Ed was about 13, those symptoms of low blood sugar disappeared. "One day it all just was gone. I never felt or saw them coming." Ed began suffering from frequent periods of "hypoglycemia unawareness," when people don't realize that their blood sugar levels are dangerously low, preventing them from eating sugar or taking medicine in response. He recalls an example while playing a football game in high school: "We were going to be undefeated, and we lost that game because I let a guy go 96 yards right down the sideline. It was an easy tackle, but I couldn't even see him I was so blind." This lack of awareness meant that Ed had no warning that he was in a dangerous situation. While many people with type 1 diabetes suffer from hypoglycemia, Ed's condition was particularly severe. He was in a minority of people with type 1 diabetes who, for reasons not fully understood, have frequent severe hypoglycemia and hypoglycemia unawareness and for whom standard blood sugar control, even with today's technology, is not sufficient.

As Ed became an adult and began work in construction, things got even worse. He'd be on a job, working fine, and then "all of a sudden I couldn't lay out a stair. I

PATIENT PROFILE

couldn't cut a roof. I couldn't cut a sheet of plywood. I'd sit there and look at my tape measure. I'd have the measurements, but I just couldn't find them on my tape measure," he recalls. "I'd be walking on top of a 28-foot wall, and I wouldn't know where I was." Or he would go to the hardware store for something, but then couldn't figure out what he was doing there. One time he found himself out of gas and parked in a stranger's front yard with no recollection of how he got there. Even keeping a supply of sugar tablets nearby didn't always help because he couldn't get to them, couldn't open them, or couldn't remember what he was trying to do.

"My family was always scared," he says. "They were always afraid that I was going to die."

All of this took a toll on Ed's family and co-workers. "My family was always scared," he says. "They were always afraid that I was going to die. It got to where my wife and daughter would know [he was having a low sugar reaction] just by looking in my eyes or by the way I was talking on the phone." They'd tell him: "Check your blood. Check your blood." Ed shares, "You get tired of hearing 'check your blood.'"

It wasn't only recognizing Ed's hypoglycemic reactions that affected his family and co-workers, but treating them as well. For example, when a low blood sugar reaction would strike "in the middle of the night, I'd be thrashing about in my bed," Ed recounts, "and my wife—who has to go to work in the morning—would try to wake me up." She would try to give him food or medicine to raise his blood sugar levels, but if she couldn't, "she'd have to call the paramedics," he says. At work Ed's crew would also look out for him. "They were relying on me, and they'd walk into my office. I'd be out of it, and they'd have to tell me: 'Ed, eat a candy bar.'" Despite all this, he remembers thinking: "It's just life, and that's how it's going to be."

Islet Transplantation: A Promising Treatment

Unbeknownst to Ed at the time, researchers at the nearby University of Illinois at Chicago were working with other researchers around the world on islet transplantation, a procedure that has the potential to restore blood sugar control to a person with type 1 diabetes, leading to insulin independence and reductions in episodes of hypoglycemia. In islet transplantation, the insulin-producing islets from a deceased organ donor are purified from the other cells in the pancreas, processed to maintain their viability and promote engraftment, and infused into the liver of the recipient. Once implanted, the islets begin to make and release insulin in response to the body's needs. This procedure may be preferable, for some people, to whole pancreas transplantation as it is less invasive, but the procedure is still considered experimental in the United States.

World experts in the field of islet transplantation, including researchers at the University of Illinois at Chicago, joined together to form the Clinical Islet Transplantation (CIT) consortium to move the field forward with innovative approaches and toward a more consistent procedure that could be approved by the U.S. Food and Drug Administration (FDA). This collaborative research group is led by the NIDDK and the National Institute of Allergy and Infectious Disease and is funded by the *Special Statutory Funding Program for Type 1 Diabetes Research*.

Ed was driving in his car when he heard a radio advertisement recruiting participants for CIT studies at the University of Illinois at Chicago. "I was listening

PATIENT PROFILE

to the sports scores…and [the ad said]: 'If you want to be cured of diabetes, give us a call.' And I figured, yeah right. I've had this for 48 years. There's no way," remembers Ed. But 5 minutes later he got a call from his brother who had heard the same ad and encouraged him to call.

Ed had to go through a rigorous screening process before being selected for the procedure. The doctors needed to confirm that Ed's diabetes was so uncontrollable with standard insulin therapy that the benefits of the transplant would outweigh the potential risks. The risks include those associated with the transplant procedure (*e.g.*, bleeding and blood clots) as well as those associated with the immunosuppressive medications that transplant recipients must take to stop the immune system from rejecting the transplanted islets. Immunosuppressive medications have significant side effects, and their long-term effects are still not fully known. Immediate side effects may include mouth sores and gastrointestinal problems, decreased kidney function, and increased susceptibility to bacterial and viral infections and cancer. In addition, there is currently no guarantee that the transplanted islets will work long-term; previous transplant recipients have lost insulin independence over time.

For the majority of people with type 1 diabetes, whose diabetes can be controlled with the ever-improving technologies that are available for managing their disease (such as advanced glucose monitors and improved forms of insulin), the risk of side effects from the immunosuppressive medications may outweigh the benefits of the transplant. Therefore, most people with type 1 diabetes are not candidates for islet transplantation. But, for people like Ed who have frequent severe hypoglycemia and hypoglycemia unawareness, the benefits of the transplant may outweigh the risks of having to take immunosuppressive medicines. The benefits might also outweigh the risks for people who have received, or who will receive, a kidney transplant and thus will need to take the immunosuppressive medications for that transplant. Islet transplantation could also be beneficial for some people who don't have type 1 diabetes—people who have had their pancreas removed due to severe pancreatitis. In this case, people could receive their own islets, rescued from any remaining healthy tissue, and not need immunosuppressive medication.

After his transplant, Ed says: "It's so magnificent, a miracle, fantastic. Never in my lifetime did I see this coming....Not only do I feel great, but my family, co-workers, friends…they're feeling better because they don't have to worry about me anymore."

The researchers determined that the benefits of the transplant outweighed the risks for Ed, so he was eligible to enroll in the trial. For him, it was an easy decision to participate. "I didn't even think about it," he confesses, "I was getting cured. This is a huge gift. How could I ever turn that down? I was thinking about no shots, no passing out. Where do I sign?"

Then began the wait for a deceased donor pancreas that would be a match for Ed. He was told that the call could come at any time, so he would need to be ready to go at a moment's notice and have a bag packed with everything he'd need for the hospital. "When you're first doing it," he remembers, "you think about it every day and night. I've got to have this, I've got to have that." But, the suitcase sat in Ed's bedroom for a

PATIENT PROFILE

year. He remembers that, after waiting for a while, he stopped thinking about it as much and began to assume that he wouldn't get the call. But then, one night that changed: "All of sudden I got a call, and [the study staff said] 'NOW. You must be here now,'" says Ed. The researchers had islets ready to transplant into him.

A New Life

Two months after the first transplant, Ed had a second islet transplant, which is not unusual. Since then, he has been insulin free, meaning that he has not needed to take insulin shots, and he no longer suffers from hypoglycemia unawareness. His life has been forever changed. "You guys don't know what you've got," he says. "I never knew what I could have had. I was 5 years old. All I remember was shots and shots, and lows and highs, and passing out here, and walking until I dropped." And now, after his transplant, Ed says: "It's so magnificent, a miracle, fantastic. Never in my lifetime did I see this coming. I don't have to worry about not waking up. I can drive, and I don't have to test my blood at stop lights. [This] turned my life around."

Ed's participation in the CIT study has not only changed his life, but also the lives of those around him. "Not only do I feel great, but my family, co-workers, friends … they're feeling better because they don't have to worry about me anymore. Everyone was so relieved. They don't have to watch me. They're not afraid anymore. My co-workers have meetings through lunchtime now," he laughs, grateful that he no longer has to schedule meetings around checking his blood sugar, taking an insulin shot, or eating.

Being part of a clinical trial is work, Ed says, "A lot of records, a lot of paperwork, and you have to show up at the times they tell you." But, he is quick to encourage others to consider participating. He is eager to give back and help others with type 1 diabetes, having seen adult friends with the disease suffer from complications. "I'm not an angel diabetic," he reflects, knowing firsthand how hard it is to check blood sugar levels continually, take insulin shots regularly, and watch what you eat diligently. "But I think I'm really like most people out there. I'd love to help other people like that and get them to understand that there's a way we can get over the hump."

To everyone involved with the islet transplantation procedures, Ed says, "You've given me a great, big gift. I can't thank you enough. My family and co-workers can't thank you enough."

For now, islet transplantation is still an experimental procedure, only allowed by the FDA as part of research trials. By developing a standardized procedure for the production of the islets for transplantation and working closely with the FDA to determine whether that procedure conducted by researchers at multiple medical centers can lead to improved blood sugar control in people with type 1 diabetes, the CIT consortium is paving the way toward making this procedure more widely available. If the research conducted by CIT is successful and leads to FDA approval, then islet transplantation would no longer be considered experimental. There will still be challenges, however, including one that Ed is hopeful will be overcome: the shortage of donated pancreata. "I hope that more people donate their organs," he shares. Beyond that, Ed is hopeful for a future without type 1 diabetes, one in which the disease is prevented outright and the devastating hypoglycemia and complications don't occur. "It would be huge," he says of preventing the disease.

PATIENT PROFILE

Ed is so grateful and thankful to everyone involved in the trial, especially the families and friends of the deceased donors who provided the pancreata. "I think about them all the time," he shares. "I say a prayer, and I thank those people whoever they are. I thank them, their families, and their friends, every morning and every night. I want to tell them how it saved my life. I want to give them a hug. I want to take them out to dinner." He'd like to tell them: "You've given me a great, big gift. I can't thank you enough. My family and co-workers can't thank you enough." Ed feels very fortunate to have participated in the CIT study and to have received this "gift." "I want to thank everyone—the people who do this: the researchers, those people who you don't even see—the ones breaking the pancreas apart and taking the cells— the nurses who work really hard and care, and the doctors. And my family. I'd like to thank all of them."

PATIENT PROFILE

Hailey Jeter

Treatment for Rare Genetic Disorder Provides Health Today and Hope for the Future

Hailey Jeter

Hailey Jeter is a mature, smart 17-year-old high school senior who is an avid reader, likes all her classes in school—especially math—and loves spending time with her three best friends. She has also bravely tackled more than most other teenagers—she has a very rare disorder called generalized lipodystrophy. "There aren't very many of us," Hailey says. It's so rare, in fact, that she's never met another person with the disorder. She and her family didn't find out that she had lipodystrophy until she was 14 years old, even though she started having health problems as a baby. But, thanks to a loving and supportive family, as well as her participation in an NIDDK clinical trial, her health is better today than it's ever been.

A Baby Who Wouldn't "Plump Up"

"It all started not long after she was born," says Hailey's mom, Kelli, remembering back to the first signs that her baby daughter was having health problems. Already an experienced mother of two other daughters, Kelli says that about a month after Hailey was born, "my husband and I noticed that she wasn't turning into the tubby little infant that our other daughters had turned into. She was eating, but she just wasn't plumping up." By the second month of Hailey's life, Kelli and her husband knew that something was wrong when their baby was losing weight and had no visible fat under her skin. Their pediatrician ordered blood work on baby Hailey and found that her sugar (glucose) and triglyceride levels were extremely high.

"It all started not long after she was born," says Hailey's mom, Kelli. "My husband and I noticed that she wasn't turning into the tubby little infant that our other daughters had turned into. She was eating, but she just wasn't plumping up."

After getting the results of the blood work and not knowing what could be causing Hailey's symptoms, the pediatrician referred the Jeters to several medical experts to determine the underlying cause. But, "no one could give us an answer," says Kelli. "At that point, all they really knew to do was to change her diet." Thus, she was told to stop nursing Hailey and to give her a special formula to help her gain weight. "And it worked," she reports, "she was starting to fill out." Even so, "her blood work was still the same. So it was a frustrating thing, and this went on for years." They

PATIENT PROFILE

were told to keep Hailey on a high-calorie, low-fat diet, and "that's how we walked through life for the first 6 years," says Kelli.

The family came close to getting a diagnosis when Hailey was 6 years old. A nutritionist who treated her as a baby transferred to a new job and got involved in research on lipodystrophy. Even though he hadn't seen Hailey since she was a baby, he remembered her and thought that she might have the disorder. However, test results were inconclusive, so the family still didn't have any answers. "So we continued to go forward with the [high-calorie, low-fat] diet," says Kelli, "and that continued for another 6 years until she was 12." But, the diet wasn't working, and Hailey's health was getting worse.

More Health Problems…But Still No Answers

When Hailey was 12 years old, she had a series of new health problems. First, she developed xanthomas, a skin condition in which fats build up under the skin. "When your triglycerides get so high, you actually break out in lesions and little bumps," explains Hailey. But, even the xanthomas were misdiagnosed—she was given cream for a viral rash, which "wasn't doing anything," she remembers. She then started having other symptoms, such as a stomach ache and fever, so her mother took her to the emergency room. There, they were told that she had pancreatitis—inflammation of the pancreas that could be life-threatening. The next blow came after Hailey went to her endocrinologist because of the recent health problems and found out that she had diabetes. She was put on insulin shots to treat the diabetes.

However, the doctors still didn't know the underlying cause of all of these health problems, so they were treating the problems as they arose. "And that's how it's been for us," explains Kelli. "It's always been 'treat the side symptoms.' It's been so frustrating."

"I was hungry all the time," says Hailey. "After I would eat, I would think about what I'd be eating next."

Having diabetes was particularly difficult for Hailey. "This is where life got hard for her," her mother states. "She's 12 years old, and she's taking 11 [insulin] injections per day." She was also taking other medications, such as drugs to lower her triglycerides, which were still very high. Hailey recalls that when she first found out that she had diabetes, "it was kind of fun to me. It was learning the shots, and I like to learn stuff." But the initial enthusiasm didn't last long, and the insulin wasn't making her feel better. "After a while, especially once we were doing all the work and weren't seeing results, that's when it got hard because I felt that I didn't want to do it [take insulin shots] anymore, but I had to," she explains.

Compounding the health problems was the fact that Hailey found out she had diabetes in 7th grade, an age when not being able to do what the other kids do can be challenging. For example, Hailey remembers that, before lunch, she'd have to leave early to go to the nurse's office for an insulin shot rather than just go to lunch with the other kids, making her stand out. And the xanthomas were getting worse, too. "It was hard on her psychologically," says her mother.

Hailey didn't have any energy and "I was hungry all the time," she says. "After I would eat, I would think about what I'd be eating next." She and her family had no idea why she was hungry all the time, and it was difficult to control her diabetes when she was constantly eating. "They would tell me to try to eat smaller portions, and I was thinking 'ok,' but once

PATIENT PROFILE

it was time to eat, I couldn't do it," she remembers. Her mother knew how difficult this was for Hailey. "Everyone was trying to get her to do something that she just didn't want to do."

A Chance Meeting Leads to an Answer

When Hailey was 13 years old, the family heard from the same nutritionist who had contacted her doctor when she was 6. All those years later, he still thought that Hailey had lipodystrophy. He told them about a clinical trial enrolling people with lipodystrophy near their home state of Ohio. However, the trial had only been going on for a short time; Kelli didn't have much information about it; and her daughter had never been diagnosed with lipodystrophy. Thus, Kelli was hesitant. She said that, with all the uncertainty and not knowing the risks, "it just didn't feel right." Still, it put lipodystrophy on the family's radar screen once again.

Meanwhile, the insulin was having less and less of an effect, so Hailey's endocrinologist kept increasing her insulin dose and, at age 14, put her on a very concentrated form of insulin. "Now here's the miracle part," says Kelli. After Hailey had been on that new insulin for a few months, a nurse at their endocrinologist's office attended a scientific conference. There, she heard a talk given by Elaine Cochran, a pediatric nurse practitioner in the NIDDK's Intramural Research Program. Hailey's nurse approached Elaine after the talk to ask her some questions. According to Kelli, "Once our nurse started explaining to Elaine some of the symptoms that Hailey was having, she [Elaine] knew right away. She said: 'I think she is one of ours.'"

About Lipodystrophy

What Elaine suspected was that Hailey had lipodystrophy—as their former nutritionist had suggested, but that had never been confirmed by their doctors. People with lipodystrophy lack fatty tissue. Depending on the extent of fat loss, lipodystrophy can be generalized (near total lack of fat) or partial (fat loss in certain parts of the body); Hailey has a genetic generalized form. Because lipodystrophy is very rare, many doctors are unfamiliar with it, so people may not be diagnosed for years.

While lipodystrophy is characterized by the loss of fatty tissue in certain areas of the body, fat accumulates in other more dangerous places, like liver and muscle, where it impairs metabolic activity. People with lipodystrophy may have very high triglyceride levels in their blood, which can lead to attacks of pancreatitis. They also have a condition called insulin resistance and thus have elevated blood sugar levels, putting them at high risk of developing diabetes.

An important consequence of lipodystrophy is a deficiency in leptin, a hormone made by fat cells. One function of leptin is to travel to a key control center in the brain to report on the body's energy stores and reduce appetite. Without adequate levels of leptin, the brain doesn't get that important signal, resulting in constant hunger, as Hailey experienced.

Leptin was first identified in 1994 by NIDDK grantee Dr. Jeffrey Friedman. Administering the hormone to obese animals lacking leptin led to weight loss, so scientists thought that leptin may be a useful therapeutic for common forms of obesity. Unfortunately, clinical trials showed that it was not effective in treating the vast majority of cases of human obesity, which are not due to leptin deficiency. Obese individuals actually have high levels of leptin, suggesting that common forms of obesity are associated with a resistance to leptin's actions. However, there are rare forms of obesity and other

PATIENT PROFILE

conditions—like lipodystrophy—in which people are leptin deficient, so researchers have examined using leptin as a therapeutic in such diseases and disorders.

Elaine's comment that Hailey could be "one of ours" stemmed from her involvement in a long-term NIDDK clinical trial being conducted at the NIH Clinical Center in Bethesda, Maryland, under the leadership of scientists in the NIDDK Intramural Research Program: former NIDDK Director Dr. Phillip Gorden and Dr. Rebecca Brown. The trial was investigating whether leptin treatment—to correct the leptin deficiency—could ameliorate conditions associated with lipodystrophy. Before leptin, people with lipodystrophy were given medicines to treat the associated health problems, but those medicines were only marginally effective—as had been Hailey's experience. The NIDDK's trial had been ongoing for over a decade and was still enrolling patients to gather more data; researchers were also publishing trial results periodically to report on the progress. Thus, by the time that the Jeters found out about the trial, published results showed that leptin treatment led to dramatic health benefits, including improved blood sugar and triglyceride levels, and reduced or discontinued need for diabetes medications.

When Kelli heard about the nurses' conversation at the scientific conference, she contacted Elaine immediately, and Elaine sent her information on research being conducted on lipodystrophy. "And there were pictures of people who actually looked like me physically," recalls Hailey, "I'd never seen anyone who looked like me." What convinced Kelli that this could finally be the answer they had been looking for was when Elaine told her about a Facebook page for people with lipodystrophy. Kelli saw photos of babies who looked exactly like Hailey had looked as a baby. "I thought: this is it, this is what she has," she remembers, "it just felt right." Elaine told Kelli about the NIDDK's clinical trial testing leptin and that Hailey could be eligible to enroll. Within 2 months, mother and daughter were at the NIH Clinical Center.

Kelli emphasizes that enrolling Hailey in the NIDDK's clinical trial "literally saved and changed her life for the better. Everything is different. Her outlook on life is different. Her confidence is different. She's happy."

A Life Changed for the Better by Participating in an NIDDK Clinical Trial

Tests at the NIH Clinical Center confirmed the suspicions that Hailey had generalized lipodystrophy. As part of the clinical trial, she was started on a treatment regimen of twice-daily leptin injections and was told she would see results in about 3 months. It didn't take that long. "In 3 weeks, we were taking her off insulin," reports her happy mother, because the leptin treatment improved her blood sugar levels without the need for insulin. Hailey remembers having a lot more energy, not being hungry all the time—and being happy. And even though she still has to take other medicines along with leptin, it is nothing like the 11 insulin shots each day that she once endured. She administers the leptin at home, so it doesn't affect her school day—she no longer needs to leave early for lunch to take medicine. "School is completely normal now," Hailey states happily.

As part of the trial, they came back to the NIH Clinical Center after 6 months and saw huge improvements in all of Hailey's test results. They came back another 6 months later, and Hailey was doing so well that the doctors said she didn't have to come back for an entire year. During that year—and based on the

positive results seen in Hailey and in other participants enrolled in the NIDDK's clinical trial—the U.S. Food and Drug Administration approved the use of leptin for treating people with generalized lipodystrophy.

Although Hailey and her family were happy about the approval and being an important part of it, it was bittersweet for them, because they would only have one more visit to the NIH before responsibility for her care was transferred to her local doctor—and Hailey loves coming to the NIH. Talking about the NIDDK's doctors and nurses who have cared for Hailey, Kelli says, "They've made us feel like we're part of their family, so we treat them that way, and we feel that way about them....we just feel like they're so much a part of her life and how she's changed." Also important to Kelli was that, "Elaine took the time to explain to me what was going on in her [Hailey's] body metabolically ... and that had never been answered before." That personal attention helped make Kelli feel comfortable with enrolling her daughter in the NIDDK's trial.

At their final visit to the NIH, there was more exciting news—Hailey was doing great. Her triglyceride and blood sugar levels were both in the normal range, and she no longer had conditions that once affected her, like diabetes, fatty liver, and xanthomas. The progress motivates Hailey to keep taking her medicines. Compared to past experiences of taking medicines and not feeling better, "It's a lot easier to take the medicine when you know it's working," she says.

Kelli emphasizes that enrolling Hailey in the NIDDK's clinical trial "literally saved and changed her life for the better. Everything is different. Her outlook on life is different. Her confidence is different. She's happy. It was just a chance meeting between Elaine and our nurse, and her whole life has changed for that reason."

Moving Forward with the Support of Family and Friends

Hailey's future is bright now that she is on medicine that is improving her health so dramatically. And Kelli has a positive outlook on the future, even though "there was a time it wasn't," she recalls, "when Hailey was younger and I thought there were just no answers." Because her daughter is doing so well, she says, "Now we can laugh. Now we can share. We have a positive outlook that we didn't have before."

And the family is looking forward. On one of their long drives from their home in Ohio to the NIH Clinical Center in Maryland, Kelli told her daughter that she felt so bad that she had to go through all that she did, and that they didn't get a diagnosis of lipodystrophy sooner. Hailey responded, "I think I needed to go through that because it makes me appreciate more the way that it ended up. I have an appreciation now for my medicine, the way that it works, for taking care of myself." Kelli was amazed by her daughter's maturity and knew right then that they would be able move forward and concentrate on the future.

Looking to that future, Hailey wants to be a nurse—being inspired by the wonderful nurses, like Elaine, who have cared for her over the years. There's no question that she will be able to draw on her intellect, maturity, family support, and personal experiences and be caring, compassionate, and empathetic toward her future patients. "She's such an outstanding person," says her proud mom.

Hailey continues to appreciate the support of her entire family, including her dad, Eric, and two older sisters, Amber and Taylor. Her mother has always been extremely supportive and continues to take some of the burden off her daughter by readying

PATIENT PROFILE

Hailey's leptin injections and putting her other medicines in a pill box. Hailey's three best friends have also been a huge support, both at home and at school, including waiting for her to take insulin before lunch so they could eat together. As Kelli explains, "Our recipe is to do what the doctors say and mix that with a lot of support from our family and her friends." She has always given her daughter an important message: "You're not different. You're special," and Hailey knows that to be true.

Hailey decided to share her personal story because she wants people to know about lipodystrophy, how serious it is, and how people with the condition should be treated with respect and compassion. "I go through a lot with kids at school," Hailey says, remembering times when her classmates didn't understand that she was living with a serious medical condition and would say unkind things to her. "I feel that if the disease was something that everybody was aware of, and at least had heard about and [understood] what we go through, then they would be more sensitive to what they say."

Hailey Jeter (center) with her sisters Taylor (left) and Amber (right)

When asked what she would say to the scientists who made leptin treatment possible, Hailey responds, "I can't say a 'thank you' that's big enough. There aren't enough words." Thinking back to all she went through, she can't imagine having to cope with those serious health problems for the rest of her life. And now, because of the support of her family and friends, and "because of NIH," she says, she doesn't have to.